BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Remarks

Claims 15-27 have been cancelled, claims 1, 14, 36 have been amended, and new claims 53-56 have been added. Support for the amendments is found throughout the specification, including, for example, at paragraphs [0038] and [0050] (ATCC Deposit No. 75804), paragraphs [0068], [0077], [0079] (fragments with activity), and the sequence listing (SEQ ID NO: 2 and 7). Thus, no new matter has been added.

Applicants note that although in the Detailed Action portion of the Office Action, the Examiner stated that "Claims 1-15, 24, 25, and 27-**54** are pending in the instant application" (see Paper No. 12, page 2, second sentence), there were previously only 52 claims in the claims set.

Claims 1-14 and 28-56 are pending.

I. Priority

On page 3 of Paper No. 12, the Examiner asserted that the present application allegedly cannot claim priority to U.S. Patent Application No. 08/459,101, now U.S. Patent 5,945,300, filed June 2, 1995, arguing that there was no "guidance of examples, prophetic or working, regarding the elected inventions drawn to a method of stimulating angiogenesis in a mammal comprising the administration of a polynucleotide encoding CTGF-2" (see Paper No. 12, page 4, first paragraph).

Applicants respectfully disagree and traverse.

Methods of administrating the claimed polynucleotide are taught in the specification of the parent, U.S. Patent Application No. 08/459,101. *See* page 21, third full paragraph. Example 3 of U.S. Patent Application No. 08/459,101 discloses a method by which a retroviral vector can be used to deliver the gene of interest to a mammalian host. One skilled in the art would be able to follow this protocol without undue experimentation to administer the polynucleotide encoding CTGF-2 to a mammal. In addition, page 21, third full paragraph, and page 23, first full paragraph, describe additional methods of polynucleotide administration. Furthermore, support for stimulation of angiogenesis can be found at page 1, second paragraph, last sentence, and page 3, first paragraph, last 2 lines, wherein wound healing, tissue repair, and stabilization of tissue implants is discussed. One of skill in the art would recognize that all these functions depend on stimulation of angiogenesis to occur. Further, page 3, sixth full paragraph, describes antagonists of CTGF polypeptides which would inhibit tumor growth. One of

skill in the art would recognize that a manner in which these antagonists would function could be by inhibiting the angiogenesis stimulated by CTGF.

In light of the above, Applicants assert that the present claimed invention is entitled to claim priority to U.S. Patent Application No. 08/459,101 under 35 U.S.C. §120. Applicants respectfully request acknowledgement of this in the next Official Action.

II. Claim Rejections – 35 U.S.C. §112, Second Paragraph

On page 4 of Paper No. 12, the Examiner rejected claims 1-14 and 28-52 under 35 U.S.C. § 112, second paragraph, due to the alleged indefiniteness of the term "derivative." *See* Paper No. 12, page 4, last paragraph.

Although Applicants disagree, claims 1,14, and 36 have been amended to remove the term "derivative," and claim 15 has been cancelled. Thus, Applicants respectfully request that the rejection be reconsidered and withdrawn.

III. Claim Rejection – 35 U.S.C. §112, first paragraph

A. Written Description

On pages 5-10 of Paper No. 12, the Examiner has rejected claims 1-14 and 28-52 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that:

> In the instant case, SEQ ID NO: 2 and 7 are the only sequences whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been the active fragment or derivative of a polynucleotide encoding CTGF-2, other than SEQ ID NO: 7.

See page 6, first paragraph of Paper No. 12.

Applicants respectfully disagree and traverse. Preliminarily, Applicants note that claims 1, 14 and 36 have been amended to remove the recitation of the terms "an active fragment or derivative thereof." Therefore, the rejection has been rendered moot with respect to these elements of the claims.

Specific enumeration of a polynucleotide encoding SEQ ID NOS: 2 and 7, the CTGF-2 polypeptide encoded by the cDNA contained in ATCC Deposit No. 75804, and a CTGF-2 polypeptide fragment with angiogenic activity has been added to claim 1. Applicants respectfully submit that the present specification contains ample disclosure for

the now-claimed embodiments for SEQ ID NOS: 2 and 7, as agreed by the Examiner (see page 6 of Paper No. 12), as well as for the CTGF-2 polypeptide encoded by the cDNA contained in ATCC Deposit No. 75804 (see paragraph [0038] of the specification) and a CTGF-2 polypeptide fragment with angiogenic activity (see paragraph [0068] of the specification). Therefore, Applicants have clearly contemplated the species within the scope of the instant claims. As a result, Applicants respectfully submit that one of ordinary skill in the art can readily recognize the members of the claimed genus.

Applicants note that the test for the written description requirement is whether one of ordinary skill in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. Further, the Federal Circuit recently re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed,'" *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000). The court emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, *rather than whether the specific embodiments had been explicitly described or exemplified.* Indeed, as the court noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Unocal*, 208 F.3d at 1001 (emphasis added). *See also, Nelson v. Bowler*, 1 USPQ2d 2076, 2078-2079 (Bd. Pat. App. & Int'f 1986) ("[W]here the claims involved are drawn to specific compounds, it is well settled that it is not necessary for a party to expressly name the compounds to comply with the written description requirement ... The issue is whether the Nelson specifications convey clearly to those skilled in the art that Nelson invented the compounds at issue ...). From the disclosure of the present invention in the specification, one of skill in the art would clearly recognize and be able to derive the claimed ranges from the specification.

Thus, since the present claims fully satisfy the written description requirement of 35 U.S.C. §112, first paragraph, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-14 and 28-52.

B. Enablement

On page 7 of Paper No. 12, claims 1-14 and 28-52 are also rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement for a method of stimulating angiogenesis in a mammal, comprising any route of administration of a polynucleotide of CTGF-2, wherein the mammal has restenosis, although the Examiner has agreed that the specification is enabling for a method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550. *See* page 7, second full paragraph of Paper No. 12.

Applicants respectfully disagree and traverse the rejection, and note that as discussed above, claims 1, 14 and 36 have been amended to remove the recitation of the terms "an active fragment or derivative thereof."

The specification teaches at page 53, paragraph [0157], the nucleic acids encoding CTGF-2 are administered to stimulate angiogenesis to mediate a therapeutic effect. One of skill in the art would recognize that the therapeutic effect would be for any condition in which angiogenesis stimulation was necessary, including restenosis and not limited to ischemia. Page 53, paragraph [0158] of the specification teaches "any of the methods for gene therapy available in the art can be used according to the present invention." One of skill in the art would be able to select a method from the art, including various routes of administration, to use in making the invention. Page 54 of the specification, at paragraphs [0162] and [0163], a variety of methods and vectors are disclosed that can be used to introduce the polynucleotides into cells. Therefore, one skilled in the art would be able to use a number of vectors, in addition to adenoviral vector pTG14550, in a variety of methods to stimulate angiogenesis to ameliorate any of a number of ailments which require angiogenesis treatment for treatment.

In the specification, page 1, paragraph [0002], and page 3, paragraph [0010], it is taught that the current invention may be used to treat restenosis. Furthermore, it has been established in the art that the same treatment can be used to ameliorate both ischemia and restenosis. *See* References AH-AJ listed on the IDS, provided herein. Therefore one of skill in the art would recognize that treatment for restenosis would be very similar, if not identical, to the treatment for ischemia which, as the Examiner acknowledged (see Paper No. 12, page 7, second full paragraph) is enabled in the specification.

Applicants respectfully note that in order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to make the claimed polynucleotides and practice a single use of the claimed polynucleotides without undue experimentation. *See, e.g.,* M.P.E.P. § 2164.01(c). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *See Fields v. Conover*, 443 F.2d 1386, 1390-91, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art.

In re Wands involved an appeal from the Board of Appeals and Patent Interferences, affirming the Examiner, rejecting immunoassay claims on the grounds that making anti-HBsAg antibodies for use in the claimed immunoassay, other than the deposited antibody, would be "unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies." *Id.* at 735, 8 U.S.P.Q.2d at 1402. Antibodies other than the one deposited were described only in terms of function and only a general method of making and using them was disclosed in the application. *See id.* The facts showed that IgM antibodies were disfavored because they tended to self-aggregate and precipitate, isolating the correct antibodies required screening hundreds of clones, and the appellant's first four attempts were unsuccessful. *See id.* at 734, 8 U.S.P.Q.2d at 1402. Nevertheless, the Federal Circuit found that the disclosure satisfied the requirements under § 112 first paragraph. The court based its decision on the fact that the invention could be practiced with "readily available starting materials using methods that are well known in the monoclonal antibody art," and because "practitioners of the art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *See id.* at 736, 8 U.S.P.Q.2d at 1406.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.* at 737, 8 U.S.P.Q.2d at 1404. Furthermore, "[t]here is no magical relation between the number of representative examples and the breadth of the claims" with respect to enablement. *In re Borkowski*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). The issue is whether polynucleotides

encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art. A more complete disclosure is not required. *See In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with 'thousands of examples' . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . .

Thus, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all 'experimentation' is 'undue' since the term 'experimentation' implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original). Applicants submit that in the instant application, since the disclosed or otherwise known methods of making polynucleotides may be used to make and then determine, without undue experimentation, whether a given polynucleotide encompassed by the claims can be used to generate a CTGF-2 polypeptide (as shown in Examples 1 and 2), or for any of the uses discussed above in Section II, the enablement requirement is fully satisfied. *See In re Wands*, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

With respect to the now-amended claims, Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make and use the claimed polynucleotides. In particular, the specification discloses methods for isolating the cDNA from the ATCC Deposit (see Examples 1-3). The specification also teaches methods for detecting angiogenesis activity (see Examples 4-5) so that one skilled in the art could take claimed fragments and screen for angiogenic activity. The specification teaches at page 53, paragraph [0157], the nucleic acids encoding CTGF-2 are administered

to stimulate angiogenesis to mediate a therapeutic effect. One of skill in the art would recognize that the therapeutic effect would be for any condition in which angiogenesis stimulation was necessary, not just human *in vivo* gene therapy for ischemia. Page 54 of the specification, at paragraphs [0162] and [0163], a variety of methods and vectors are disclosed that can be used to introduce the polynucleotides into a variety of cells, not just for human *in vivo* gene therapy. Example 12 of the specification shows angiogenesis stimulation data from the *in vivo* delivery of CTGF-2. This one example alone meets the requirement of enabling one of ordinary skill in the art a single use for the claimed polynucleotides with undue experimentation.

The Examiner's objection to the invention due to its potential use for human gene therapy is improper. We remind the Examiner that Applicant does not need to show FDA approval for success in treating human patients by an invention:

> The Federal Circuit Court has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.
>
> M.P.E.P. §2107.01

Furthermore, the specification teaches not only a method by which to obtain the invention, but also shows examples of the invention being useful in stimulating angiogenesis. *See* Examples 7-12 of the specification. Therefore, the Examiner's reasoning that the invention is unpatentable because gene therapy cannot not be done, is flawed, since the specification clearly shows that it is possible. Moreover, it is known in the art that gene therapy is a promising method of treatment for both ischemia and restenosis. *See* References AI and AJ listed on the IDS.

Moreover, the Examiner cites portions of four references to support the position that human gene therapy is experimental and unpredictable, with the implication that therefore it is not patentable.

The Examiner uses the Anderson (1998) reference in an attempt to undermine human gene therapy. *See* Paper No. 12, first full paragraph. However, the Examiner fails to mention that this same article states that there are over 300 clinical protocols for gene therapy that have been approved (see Anderson, page 29, first paragraph). This fact clearly shows that there is no lack of guidance in the art for pursuing gene therapy strategies. Moreover, the article predicts success for gene therapy in the next five years, and "[I]n a time frame of 5-15 years from now, I expect that the number of gene-therapy

products will begin to increase exponentially" (see Anderson, 1998, page 30, second and third paragraphs). Therefore, quite contrary to the Examiner's conclusions from the quotations from this article, when placed in context, this reference predicts the enormous success of gene therapy.

The Examiner cites Anderson (2002), stating that the author "assert[s] that the reason that gene therapy has been so long in coming is because successful gene therapy in human patients is much more complex than obtaining success in treating mice" (see Paper No. 12, page 8, second full paragraph). Applicants note, in that very same article, page 1262, right hand column, second paragraph, that the author states that "And so, quietly, with little of the press coverage that occurred before, investigators have gone about making the improvements necessary for success. The incremental changes do not make headlines, but they are, nonetheless, vital," implying the little-known but on-going success in gene therapy. The author further predicts success for gene therapy. On page 1262, left hand column, first paragraph, he states, "Thus, at these meetings in 2005, three years from now, I believe we will have an FDA-approved treatment in the clinics." Again, when placed in context, Anderson (2002) is mainly enthusiastic about the wide range and future success of gene therapy.

The Examiner cites Crystal in a further attempt to show the unpredictability of gene therapy. *See* Paper No. 12, page 8, last paragraph. However, very clearly, in the first sentence of the abstract of this reference, the author states that "[E]nough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic responses that are relevant to human disease, and can provide important insights into human biology." It is further stated that "[A]dverse events have been uncommon" (see Abstract, second sentence). The article also states that "[P]robably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible.... most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies." *See* page 405, right hand column, second paragraph. This article also describes the various studies that showed successful gene transfer from page 405, right hand column, last paragraph, to the top of page 407. Table 1 of the article summarizes the numerous studies in which there was *in vivo* evidence of gene transfer, and Table 2 shows studies in which the transfer of genetic

material has evoked a biologic response. Applicants respectfully note that the one sentence that the Examiner quotes from the Crystal article is not in its proper context, and does not reflect the author's conclusions or viewpoint about gene therapy. The Crystal article actually provides overwhelming data and support for the use and success of gene therapy.

Finally, the Examiner cited the Branch article to illustrate that "the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues" (see Paper No. 9, first full paragraph). Applicants note that the Branch article is a review of antisense RNA technology, rather than gene therapy *per se*. The nature of antisense molecules are entirely different from the that of gene delivery vectors. The abstract of the article states that "they [antisense molecules] are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven." This statement alone reveals the differing nature of antisense molecules. Gene delivery vehicles are easily produced and routine techniques for one of skill in the art, and their use in manipulating the functions of genes, ranging from protocols as simple as transfecting a gene delivery vector into a prokaryotic host to produce the gene of interest to as complex as producing a knock-out mouse, has been firmly established in the art. The Branch article has little to do with gene therapy with vectors and does not contribute any argument for or against human gene therapy.

In conclusion, the teachings in the specification do indeed provide guidance for delivery of the invention in a variety of vectors to treat a variety of ailments through gene therapy. In addition, the above references do not show "lack of predictability associated with *in vivo* delivery of nucleic acids" as the Examiner alleges (see Paper No. 12, page 9, last sentence). Rather, these references are very enthusiastic about the success of gene therapy, and refer to over 300 clinically approved protocols for gene therapy and almost 40 studies in which gene therapy has been successful, leading one skilled in the art to find a plethora of guidance in the art as well as predictability.

Moreover, these references, regardless of their conclusions about human gene therapy, are not germane to the patentability of the present invention. The specification need only enable one of skill in the art for a single use for the invention to be patentable (*see, e.g.,* M.P.E.P. § 2164.01(c)), and Example 12 of the specification meets this requirement.

In view of the foregoing, Applicants submit that the pending claims fully meet the enablement requirements of 35 U.S.C. § 112, first paragraph, and respectfully request that the Examiner's rejection of the claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

IV. Claim Rejections – 35 U.S.C. §102

The Examiner has rejected claims 1, 2, 7, 9, 13, 31, and 35 under 35 U.S.C. 102(b) as allegedly being anticipated by Babic, et al.:

> Babic et al. disclose that CYR61 (CTGF-2), promotes angiogenesis in a rat corneal pocket assay (see Abstract). Babic et al. further disclose that full length mouse CYR61 cDNA was constructed in pL61SN vector, administered into the rat cornea, and neovascularization was induced (see Figure 2 and Table 1). Thus, Babic et al. anticipate claims 1, 2, 7,9, 13, 31, and 35.

Applicants respectfully disagree and traverse.

First, as discussed above, Applicants respectfully submit that the present claimed invention is entitled to priority of the parent application (U.S. Patent Application No. 08/459,101) as well as the PCT filed July 12, 1994. Therefore, Babic et al. (1998) cannot be considered prior art.

Second, assuming *arguendo* that Babic et al. is properly considered prior art against the claimed invention (which Applicants are not conceding), Babic et al. does not meet the legal requirements to make a *prima facie* case of anticipation.

M.P.E.P. §2131 at page 2100-69 states that "to anticipate a claim, the reference must teach every element of the claim." Babic et al. does not fit this description. Babic et al. did not administer full length mouse CYR61 cDNA in a pL61SN vector, as suggested by the Examiner. Rather, Babic et al, used purified CYR61 protein carried by Hydron pellets (*See* Babic et al., page 6356, right-hand column, first full paragraph, page 6357, Table 1, and page 6358, right-hand column, first full paragraph, sentence 4). This method of administration is not relevant to the claimed invention, which uses polynucleotides, not purified protein as used in Babic et al. Since Babic et al. does not teach each and every element of the claims, Babic et al. cannot anticipate the present invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

Entry of the above amendment is respectfully solicited. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an additional extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Dated: December 23, 2003

Respectfully submitted,

By _____

Mark J. Hyman
Registration No.: 46,789
HUMAN GENOME SCIENCES, INC.
9410 Key West Avenue
Rockville, Maryland 20850
(240)314-1224

MJH/KN/ba